Remarks

Claims 1 to 21 were in the application as filed. Claims 1 to 21 were canceled and Claims 22 to 33 were added in the Preliminary Amendment filed on September 10, 2003.

Claims 22 to 24, 29 and 31 to 33 have been amended to comport these claims with U.S. claim format.

Claim 22 has been amended to insert the word "in" to correct an inadvertent grammatical error presented in the Preliminary Amendment dated September 10, 2003.

Claims 31 to 33 have been amended to clarify that these claims refer to methods of treatment and to change their dependencies to Claims 34 to 36, respectively. Support for these amendments can be found, for example, on page 24, line 18 to page 26, line 5, of the Specification and in the original claims.

Claims 34 to 36 have been added by the foregoing amendments. Support for Claims 34 and 35 can be found, for example, on page 24, line 18 to page 26, line 2 of the Specification. Support for Claim 36 can be found, for example, on page 26, lines 3 to 5 of the Specification.

Claim 22 has been amended to cancel the non-elected subject matter of Groups II to IV, VI to VIII and X to XII.

Claim 30 has been canceled by the foregoing amendment.

Applicants reserve the right to pursue the canceled subject matter in pending or future divisional, continuation or continuation-in-part applications.

No new matter has been added by these amendments.

As presently amended, Claims 22 to 29 and 31 to 36 are pending in this application.

Information Disclosure Statement

The Examiner states that the references cited in the Information Disclosure Statement (IDS) filed on September 10, 2003 have not been considered as the IDS fails to comply with 37 C.F.R. §§ 1.97, 1.98, and MPEP 609.

Pursuant to 37 C.F.R. §1.98(d), copies of the listed references are not required if they were previously cited by or submitted to the United States Patent and Trademark Office (USPTO) in a prior application which is relied upon for an earlier filing date under 35 U.S.C. §120. As was previously pointed out by Applicants in the IDS submitted on September 10, 2003, the listed references were previously cited by or submitted to the USPTO in prior application Serial No. 09/722,361, filed November 28, 2000, which is relied upon for an earlier filing date under 35 U.S.C. §120. Attached Exhibit A is a copy of the Notice of References Cited issued by the USPTO in the parent Patent Application Serial Number 09/722,361. All of the references cited in the IDS submitted in the present case on September 10, 2003 are contained in Exhibit A. Accordingly, no basis is seen for the Examiner's assertion that the previously submitted IDS does not comply with 37 C.F.R. §§ 1.97, 1.98, and MPEP 609. Thus, Applicants respectfully request that the Examiner consider the cited references.

Nevertheless, solely for the Examiner's convenience, Applicants submit herewith copies of the references listed in the IDS filed September 10, 2003.

Objections

The Examiner has objected to the Specification as being allegedly informal for the stated reason that the reference listed in Example 15 does not exist.

The reference listed in Example 15 for the preparation of 4,6-diamino-1-methylquinoline (J. Chem. Soc., 1953, 50) does exist. Applicants attach a copy of this reference for the Examiner's convenience (Exhibit B). Therefore, reconsideration and withdrawal of this objection is respectfully requested.

Rejections under 35 USC § 112, First Paragraph

Claims 22 to 33 rejected under 35 U.S.C. 112, first paragraph, as being, the Examiner alleges, non-enabled for the given reason that the specification, while being enabling for the core where the nitrogen-containing aromatic ring and the aromatic ring are both quinoline and the distribution agent is a diazine (pyrimidine, pyrazine, or pyridazine), does not reasonably provide enablement for compounds not covered by this group (Office Action page 4).

This rejection is rendered moot in view of the above-described amendment to Claim 22, cancelling the non-elected subject matter. Accordingly, withdrawal of this rejection is respectfully requested.

Claim 26 is rejected as being non-enabled for methods of treating all forms of cancer. The Examiner maintains that "Applicants have to show testing for each and every different cell line for cancer to be enabled for this method of use" (Office Action, page 5).

It is respectfully submitted that Claim 26 is fully enabled pursuant to the provisions of 35 U.S.C. 112, first paragraph as the Specification clearly teaches how to make the compounds of the invention and how to use these compounds for the treatment of cancer.

Nevertheless, Applicants traverse the rejection and reconsideration and withdrawal thereof are respectfully requested for the reasons given hereinbelow.

The Specification describes the link between inhibiting telomerase activity via the stabilization of G-quadruplexes for the treatment of cancer (pages 2 to 4). The Specification further details how to evaluate the G-quadruplex activity and the anti-telomerase biological activity, and provides the results obtained for numerous compounds of the invention in Example 17 (pages 55 to 58). The Specification also describes the procedures for evaluating the cytotoxic activity on human tumor cell lines, and again provides the results of such experiments for numerous compounds of the invention in Example 17. Therefore, Applicants have provided data showing the G-quartet, antitelomerase, and cytotoxic activity of various compounds of the invention and have described the nexus of such activity with the treatment of cancer. Consequently, Applicants have provided more than sufficient enablement in the Specification for the use of the instantly claimed compounds in the treatment of cancer.

The Examiner notes that each type of cancer is composed of one or more cell lines and concludes that in order for a method of treating cancer to be enabled, "Applicants would have to show testing in each and every cell line for cancer" (Office Action, page 5, emphasis added). However, Applicants are unaware of any requirement in the law that requires such evidence. Only objective enablement is required under the patent statute.

In view of the foregoing discussions, there is a significant amount of evidence of record demonstrating that the claimed compounds would be considered useful for the treatment of

cancer. Therefore, the 35 U.S.C. § 112, first paragraph rejection of Claim 26 is believed unwarranted and should be withdrawn.

There being no remaining issues, this application is believed in condition for favorable reconsideration and early allowance, and such actions are earnestly solicited.

The Commissioner is hereby authorized to charge any additional fees which may be required by this paper, or credit any overpayment to Deposit Account No. 18-1982.

Respectfully submitted,

June 26, 2007
Date

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Attorney for Applicant

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Sanofi-Aventis Docket No. ST99049G1 US DIV

EXHIBIT A

Notice of References Cited	Application/Control No. 09/722,361	Applicant(s)/Patent Under Reexamination MAILLIET ET AL.	
	Examiner Richard L. Raymond	Art Unit 1624	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

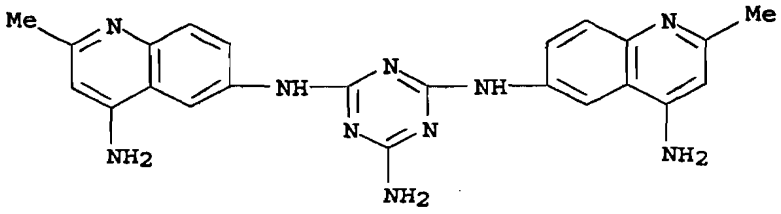
FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

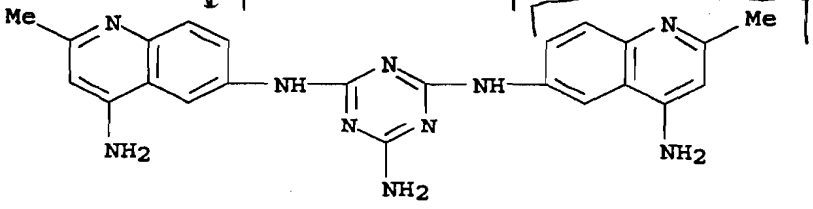
*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Gill , Chemical Abstracts, Vol. 76:94467, 1972.
	V	Burton et al., Chemical Abstracts, Vol. 118:96775, 1993.
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.



●3 HCl

L9 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1972:94467 CAPLUS
DOCUMENT NUMBER: 76:94467
TITLE: Surra. 3. Activity of certain derivatives of acridine, sulfonated naphthylamine, aminoquinaldine, styryl-quinoline, and nitrofurazone against Trypanosoma evansi in rats
AUTHOR(S): Gill, B. S.
CORPORATE SOURCE: Indian Vet. Res. Inst., Izatnagar, India
SOURCE: Indian J. Anim. Sci. (1971), 41(6), 503-9
CODEN: IJLAA4
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Quinapyramine [4-amino-6-(2-amino-6-methyl-4-pyrimidylamino)quinaldine 1,1'-dimethosulfate](I) [3270-78-8], surfen [3811-56-1], surfen C [**33608-18-3**], stryxyl [33522-68-8], nitrofurazone [59-87-0], acriflavine [6034-59-9], and trypan blue [72-57-1] were tested against Trypanosoma evansi infection in rats and, except for I, i.p., the other compds. had limited use. A few rats treated with surfen or I had secondary relapses of infection. This was not due to a decrease in virulence of the parasite.
IT **33608-18-3**
RL: BIOL (Biological study)
(Trypanosoma evansi infestion treatment by)
RN 33608-18-3 CAPLUS
CN 1,3,5-Triazine-2,4,6-triamine, N,N'-bis(4-amino-2-methyl-6-quinolinyl)-, trihydrochloride (9CI) (CA INDEX NAME)



●3 HCl

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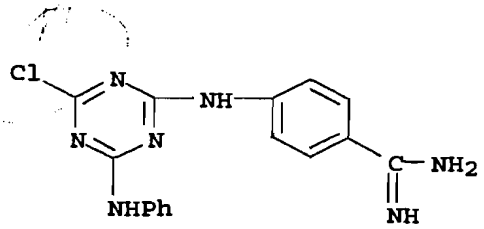
L4 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:96775 CAPLUS
DOCUMENT NUMBER: 118:96775
TITLE: Design of novel affinity adsorbents for the purification of trypsin-like proteases
AUTHOR(S): Burton, Nicolas P.; Lowe, Christopher R.
CORPORATE SOURCE: Inst. Biotechnol., Univ. Cambridge, Cambridge, CB2 1QT, UK
SOURCE: J. Mol. Recognit. (1992), 5(2), 55-68
CODEN: JMORE4; ISSN: 0952-3499
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A no. of ligands for the selective purifn. by affinity chromatog. of the trypsin-like protease, porcine pancreatic kallikrein, were designed de novo by computer-aided mol. design. The ligands were designed to mimic the side-chains of a no. of arginyl dipeptides and included a benzamidine moiety substituted on a triazine ring. The ligands displayed inhibitory activities against pancreatic kallikrein which mirrored the specificity consts. of the dipeptides they were designed to mimic. The ligand with the highest affinity for the enzyme, an analog of a Phe-Arg dipeptide, when immobilized to Sepharose CL-4B via a hexamethylene spacer arm, purified pancreatic kallikrein 110-fold in one step from a crude pancreatic acetone ext.

IT **146004-61-7P 146004-65-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of and kallikrein and trypsin purifn. using)

RN 146004-61-7 CAPLUS
CN Benzenecarboximidamide, 4-[[4-chloro-6-(phenylamino)-1,3,5-triazin-2-yl]amino]- (9CI) (CA INDEX NAME)



RN 146004-65-1 CAPLUS
CN Benzenecarboximidamide, 4-[[4-[(6-aminohexyl)amino]-6-(phenylamino)-1,3,5-triazin-2-yl]amino]- (9CI) (CA INDEX NAME)

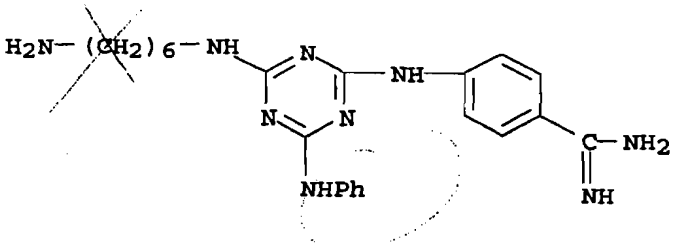


EXHIBIT B

8. *The Synthesis of Trypanocides. Part I. Some Pyrimidylaminoquinoline Derivatives.*

By P. A. BARRETT, (the late) F. H. S. CURD, and W. HEPWORTH.

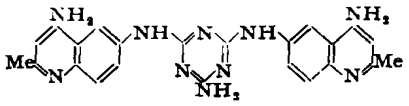
A series of compounds in which pyrimidine derivatives are linked to a quinoline nucleus through a 6-amino-group in the latter are described. The derivatives used included 2-amino-4-chloro-6-methyl-, 4-amino-2-chloro-6-methyl-, and 2 : 6-diamino-4-chloro-pyrimidine; and 6-amino- and 6-amino-2-methyl- and 4 : 6-diamino-2-methyl-quinolines. Quaternary salts obtained by the action of methyl iodide on the pyrimidylaminoquinolines were identical with those obtained by condensation of the corresponding quaternary 6-amino-1-methylquinolinium salts with the chloropyrimidines listed above.

IN this series of papers we report the chemical aspects of an investigation directed towards the discovery of new trypanocides. The chemotherapeutic aspects will be described elsewhere in collaboration with Dr. D. G. Davey.

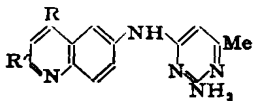
At the start of our investigation there appeared to be three main outstanding problems in the chemotherapy of trypanosomiasis: the discovery of a satisfactory drug for the treatment of human sleeping sickness in its late stages when the central nervous system has become involved, the therapy of S. American trypanosomiasis (Chagas disease) which is caused by *Trypanosoma cruzi*, and the treatment of *T. congolense* infections in cattle. Of these, the last appeared to be the most important since no completely satisfactory drug has been discovered, although considerable progress has recently been made by the introduction of the phenanthridine derivatives Phenidium Chloride and Dimidium Bromide.

Before the introduction of the above phenanthridine compounds, some experiments had been reported with a compound named Surfen C (I) (for references see Bureau of Hygiene and Tropical Diseases, Review Monograph No. 1, 1946: "A survey of recent work on trypanosomiasis and tsetse flies," p. 39). According to Jensch (*Angew. Chem.*, 1937, **50**, 891), this was discovered during a systematic investigation of derivatives of 4-amino-quinoline. He emphasised the importance of the 4-amino-group and noted the similarity of the tautomeric system in this type of compound to that found in several chemotherapeutically active 5-amino-acridines.

In our researches, which commenced with compounds of types (II and III; R = NH_2, R′ = Me), we sought to simplify the molecule of Surfen C by eliminating the triazine residue which appeared merely to act as a linking group between the two quinoline residues, and to replace one of these by an aminopyrimidine system exhibiting similar tautomeric possibilities.



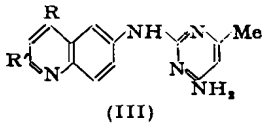
(I)



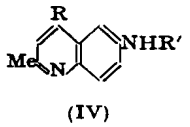
(II)

4-Amino-6-(2-amino-6-methyl-4-pyrimidylamino)-2-methylquinoline (II; R = NH_2, R′ = Me) was synthesised by condensation of 4 : 6-diamino-2-methylquinoline (IV; R = NH_2, R′ = H) with 2-amino-4-chloro-6-methylpyrimidine in boiling aqueous solution in presence of hydrochloric acid. In order to prove that condensation had taken place at the 6- and not at the 4-amino-group of the 4 : 6-diamino-2-methylquinoline, 2-amino-4-chloro-6-methylpyrimidine was condensed with 6-amino-4-hydroxy-2-methylquinoline (prepared by hydrolysis of the 6-acetamido-derivative) to give 6-(2-amino-6-methyl-4-pyrimidylamino)-4-hydroxy-2-methylquinoline (II; R = OH, R′ = Me) which was converted by phosphoryl chloride into the 4-chloro-compound (II; R = Cl, R′ = Me) and thence by ammonia in phenol into (II; R = NH_2, R′ = Me), identical with the product made by the first method. Analogously, condensation of 4-amino-2-chloro-6-methylpyrimidine with 4 : 6-diamino-2-methylquinoline gave (III; R = NH_2, R′ = Me).

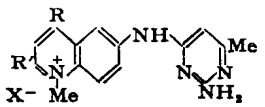
The preparation of 4 : 6-diamino-2-methylquinoline by the action of ammonia in phenol on 6-acetamido-4-chloro-2-methylquinoline (IV; R = Cl, R′ = Ac) followed by hydrolysis of the resulting 4-amino-compound (IV; R = NH_2, R′ = Ac) was described in B.P. 414,105, and this method has been used for the present work. The synthesis of (IV; R = Cl, R′ = Ac) was not described in detail in the patent and for the present work we have used Kermack and Weatherhead's procedure (*J.*, 1939, 563).



(III)



(IV)

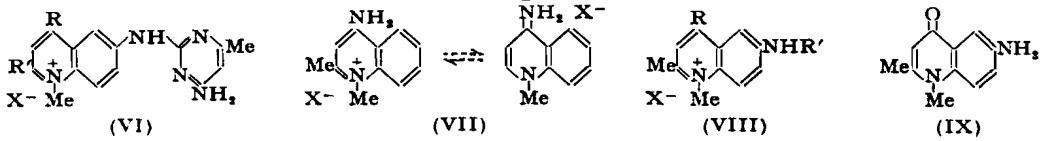


(V)

Since (II; R = NH_2, R′ = Me) and (III; R = NH_2, R′ = Me) possessed only slight trypanocidal activity, attention was directed to the corresponding quaternary salt derivatives (V and VI; R = NH_2, R′ = Me). In these substances the tautomeric possibilities of the 4-amino-2-methylquinoline system are lost, but ionic resonance is still

theoretically possible (as in VII), and resonance is of greater importance for biological activity than prototropy (Curd, Landquist, and Rose, *J.*, 1947, 154; Curd, Davis, Hoggarth, and Rose, *ibid.*, p. 783). Moreover, conversion of a heterocyclic nitrogen atom in an inactive or a slightly active structure into the quaternary state can lead to marked trypanocidal activity (cf. Browning, Morgan, Robb, and Walls, *J. Path. Bact.*, 1938, **46**, 203).

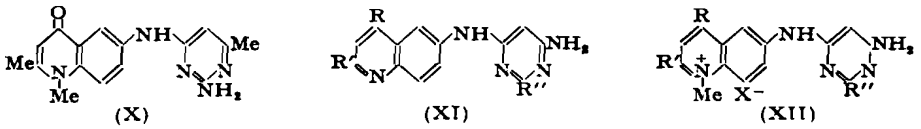
4-Amino-6-(2-amino-6-methyl-4-pyrimidylamino)-1 : 2-dimethylquinolinium iodide (V; R = NH_2, R′ = Me, X = I) and the isomeric iodide (VI; R = NH_2, R′ = Me, X = I) were first prepared by the action of boiling alcoholic methyl iodide on (II and III; R = NH_2, R′ = Me) respectively. That quaternisation had occurred on the quinoline nitrogen atom was proved by the synthesis of (V; R = NH_2, R′ = Me, X = I) from 4 : 6-diamino-1 : 2-dimethylquinolinium chloride (VIII; R = NH_2, R′ = H, X = Cl) and 2-amino-4-chloro-6-methylpyrimidine, and of (VI; R = NH_2, R′ = Me, X = I) in a similar manner, 4-amino-2-chloro- being used in place of 2-amino-4-chloro-6-methylpyrimidine. The proof depended, however, on confirmation of the structure of (VIII; R = NH_2, R′ = H, X = Cl). This compound was synthesised by treatment of 6-acetamido-4-amino-2-methylquinoline with methyl sulphate in nitrobenzene at 100°, followed by hydrolysis of the resulting methosulphate (VIII; R = NH_2, R′ = Ac, X = SO_4Me) with boiling hydrochloric acid. That it does in fact possess the structure assigned to it was proved by its hydrolysis with N-sodium hydroxide to a compound possessing the *N*-methylquinolone structure: 6-amino-1 : 2-dimethylquinol-4-one (IX). Boiling 2N-sodium hydroxide similarly hydrolyses (V; R = NH_2, R′ = Me, X = I) to (X), which was also prepared by reaction between 6-amino-1 : 2-dimethylquinol-4-one and 2-amino-4-chloro-6-methylpyrimidine.



(VI) (VII) (VIII) (IX)

The investigation was then extended to the preparation of (XII; R = NH_2, R′ = R″ = Me, X = I) and (XII; R = R″ = NH_2, R′ = Me, X = I). The former was made by two methods: condensation of 4 : 6-diamino-2-methylquinoline with 6-amino-4-chloro-2-methylpyrimidine to give (XI; R = NH_2, R′ = R″ = Me), followed by quaternisation with methyl iodide in boiling alcohol; and by condensation of 4 : 6-diamino-1 : 2-dimethylquinolinium chloride with 6-amino-4-chloro-2-methylpyrimidine followed by conversion into the iodide. The second compound resulted from the reaction of (VIII; R = NH_2, R′ = H, X = Cl) with 4-chloro-2 : 6-diaminopyrimidine in acetic acid at 150—160°. 4-Amino-6-(2 : 6-diamino-4-pyrimidylamino)-2-methylquinoline was obtained by reaction of 4 : 6-diamino-2-methylquinoline with 2 : 6-diamino-4-chloropyrimidine.

Concurrently, and for comparative purposes, we prepared by similar methods a number of analogous substances lacking the 4-amino-group in the quinoline nucleus; these included 6-(2-amino-6-methyl-4-pyrimidylamino)-1 : 2-dimethylquinolinium chloride (V; R = H, R′ = Me, X = Cl), the iodide (VI; R = H, R′ = Me, X = I) of its isomer, the



(X) (XI) (XII)

corresponding quinoline derivatives (V and VI; R = R′ = H, X = I), and 6-(6-amino-2-methyl-4-pyrimidylamino)- (XII; R = R′ = H, R″ = Me, X = I) and 6-(2 : 6-diamino-4-pyrimidylamino)-1-methylquinolinium iodide (XII; R = R′ = H, R″ = NH_2, X = I).

The 6-aminoquinoline and 6-amino-2-methylquinoline quaternary salts used were

prepared from 6-acetamido-quinoline and -2-methylquinoline by methyl sulphate in nitrobenzene, followed by hydrochloric acid. 6-Amino-1 : 2-dimethylquinolinium iodide was obtained by essentially this method by Browning, Cohen, Ellingworth, and Gulbransen (*Proc. Roy. Soc.*, 1926, *B*, **100**, 293) but neither this nor the corresponding chloride was adequately characterised. Attempts to prepare 6-amino-1-methylquinolinium iodide by Claus and Schnell's method (*J. pr. Chem.*, 1896, **53**, 119), by reaction of 6-aminoquinoline and methyl iodide under pressure, or by reaction in benzene or *via* the methosulphate gave unsatisfactory products.

Experimental

6-Acetamido-4-amino-1 : 2-dimethylquinolinium Salts (VIII; R = NH_2, R′ = Ac, X = Hal).—6-Acetamido-4-amino-2-methylquinoline (4·5 g.) was dissolved in nitrobenzene (40 c.c.) at 100° and methyl sulphate (2·8 g.) added during 5 minutes with stirring, which was continued at this temperature for 1 hour. The precipitated methosulphate was collected, after cooling, washed free from nitrobenzene with acetone, and dried. It was then dissolved in the minimum quantity of water, treated with carbon and filtered, and the filtrate saturated with sodium chloride. The precipitated *chloride* crystallised from 95% alcohol in colourless needles (yield, 59%), m. p. 318° (Found : C, 55·2; H, 6·5; N, 14·5; Cl′, 12·8. $C_{13}H_{16}ON_3Cl,H_2O$ requires C, 55·0; H, 6·3; N, 14·8; Cl′, 12·5%). It was converted into the corresponding *iodide* by dissolving it in water and adding potassium iodide. This salt crystallised from 50% aqueous alcohol as colourless needles, m. p. 294—295°, with softening from 285° (Found : C, 42·1; H, 4·7; N, 11·4; I′, 33·8. $C_{13}H_{16}ON_3I,H_2O$ requires C, 41·6; H, 4·8; N, 11·2; I′, 33·9%).

4 : 6-Diamino-1 : 2-dimethylquinolinium Chloride (VIII; R = NH_2, R′ = H, X = Cl).—The above methosulphate (4·4 g.) was dissolved in 20% hydrochloric acid (15 c.c.), and the solution boiled for 10 minutes and then cooled. The solid which separated was collected, washed with acetone, and crystallised from 20% hydrochloric acid to give the *hydrochloride* of (VIII; R = NH_2, R′ = H, X = Cl) as almost colourless prisms, m. p. 292—293° (Found : C, 51·0; H, 5·85; N, 16·25; Cl, 27·4. $C_{11}H_{14}N_3Cl,HCl$ requires C, 50·8; H, 5·8; N, 16·2; Cl, 27·3%). An aqueous solution of the above hydrochloride was made alkaline to Brilliant-yellow with sodium carbonate, and a little sodium chloride added to give the *chloride* (VIII; R = NH_2, R′ = H, X = Cl), which crystallised from 95% alcohol as yellow laminæ, m. p. 300—301° (Found : C, 55·0; H, 6·4; N, 17·6; Cl′, 15·0. $C_{11}H_{14}N_3Cl,H_2O$ requires C, 54·7; H, 6·6; N, 17·4; Cl′, 14·7%).

6-(2-Amino-6-methyl-4-pyrimidylamino)-4-hydroxy-2-methylquinoline (II; R = OH, R′ = Me).—6-Amino-4-hydroxy-2-methylquinoline dihydrochloride (6·45 g.), 2-amino-4-chloro-6-methylpyrimidine (4·6 g.) (Gabriel and Colman, *Ber.*, 1899, **32**, 2924), and water (20 c.c.) were refluxed together for 6 hours. The resulting cooled solution was made alkaline with ammonia, and the precipitated product filtered off, washed with water, and dried (yield, 7·8 g.). Crystallised from aqueous 2-ethoxyethanol, the *compound* (II; R = OH, R′ = Me) formed very pale yellow needles, m. p. 356—357° (decomp.) (Found : C, 56·45; H, 6·1; N, 22·2. $C_{15}H_{15}ON_5,2H_2O$ requires C, 56·75; H, 6·0; N, 22·1%).

6-(2-Amino-6-methyl-4-pyrimidylamino)-4-chloro-2-methylquinoline (II; R = Cl, R′ = Me).—The preceding compound (10 g.) and phosphoryl chloride (20 c.c.) were mixed. When the resulting vigorous reaction had subsided the mixture was refluxed for 20 minutes, then cooled and poured into dilute sodium hydroxide (250 c.c.). The resulting product was collected, washed alkali-free with water, and crystallised from dry methanol to give the *chloro*-compound (6·3 g.) as almost colourless needles, m. p. 254° (Found : C, 60·0; H, 5·0; N, 23·3. $C_{15}H_{14}N_5Cl$ requires C, 60·3; H, 4·7; N, 23·4%).

4-Amino-6-(2-amino-6-methyl-4-pyrimidylamino)-2-methylquinoline (II; R = NH_2, R′ = Me).—(*a*) 4 : 6-Diamino-2-methylquinoline (13·2 g.), 2-amino-4-chloro-6-methylpyrimidine (10·8 g.), water (150 c.c.), and 36% hydrochloric acid (18 c.c.) were refluxed together for 1 hour, and the reaction mixture cooled and made just alkaline with ammonia. On addition of a little sodium chloride, the *hydrochloride* rapidly separated and was filtered off and crystallised from 50% aqueous alcohol; colourless fine needles, m. p. 345° (decomp.) (Found : C, 55·9; H, 5·5; N, 26·0; Cl, 10·8. $C_{15}H_{16}N_6,HCl,0{\cdot}5H_2O$ requires C, 55·3; H, 5·5; N, 25·8; Cl, 10·9%). The *base*, obtained by treating a solution of the hydrochloride with sodium hydroxide, crystallised from 60% alcohol as colourless needles, m. p. 299—300° (Found : C, 60·1; H, 6·0; N, 28·2. $C_{15}H_{16}N_6,H_2O$ requires C, 60·4; H, 6·0; N, 28·2%). The base formed different hydrates of the same m. p. When the monohydrate was boiled with a little absolute alcohol

it dissolved but denser *anhydrous* base was deposited immediately; m. p. 302—303° (Found : C, 64·0; H, 5·8; N, 30·0. $C_{15}H_{16}N_6$ requires C, 64·3; H, 5·7; N, 30·0%).

(*b*) 6-(2-Amino-6-methyl-4-pyrimidylamino)-4-chloro-2-methylquinoline (4·3 g.) was dissolved in phenol (8 g.), the solution heated to 100°, and ammonia passed in briskly. The temperature rose to 120° and then began to fall. At this stage, with continued passage of ammonia, the temperature was raised to, and kept at 180° for 3 hours. The mixture was then cooled somewhat and poured into dilute sodium hydroxide. The resulting precipitate was collected, washed alkali-free with water, and crystallised from 50% aqueous alcohol (Found: C, 58·3; H, 6·5; N, 27·1. $C_{15}H_{16}N_6,1{\cdot}5H_2O$ requires C, 58·6; H, 6·2; N, 27·3%) to give, after dehydration as above, the same material as in (*a*), m. p. and mixed m. p. 299—300°.

4-*Amino*-6-(2-*amino*-6-*methyl*-4-*pyrimidylamino*)-1 : 2-*dimethylquinolinium Salts* (V; R = NH_2, R′ = Me, X = Hal).—(*a*) 4-Amino-6-(2-amino-6-methyl-4-pyrimidylamino)-2-methylquinoline (8 g.), methyl iodide (14 c.c.), and alcohol (100 c.c.) were refluxed together on the steam-bath for 6 hours. The mixture was cooled and filtered, and the residue crystallised from 50% aqueous alcohol to constant m. p. (at least three crystallisations were usually required) to give the *iodide* (V; R = NH_2, R′ = Me, X = I) as very pale yellow fine needles, m. p. 322—323° (Found : C, 42·5; H, 4·9; N, 18·3; I′, 28·3. $C_{16}H_{19}N_6I,2H_2O$ requires C, 41·9; H, 5·0; N, 18·3; I′, 27·7%).

(*b*) A mixture of 4 : 6-diamino-1 : 2-dimethylquinolinium chloride (5·6 g.), 2-amino-4-chloro-6-methylpyrimidine (3·6 g.), water (50 c.c.), and 36% hydrochloric acid (6 c.c.) was heated to boiling. Solution occurred, followed almost immediately by separation of colourless material. The reaction was completed on the steam-bath (1 hour), the mixture then cooled and filtered and the product crystallised from alcohol–water (3 : 1) to give needles of the *hydrochloride* of the chloride (V; R = NH_2, R′ = Me, X = Cl), m. p. 351—352° (Found: C, 50·2; H, 5·7; N, 21·8; Cl′, 18·7. $C_{16}H_{19}N_6Cl,HCl,H_2O$ requires C, 49·9; H, 5·7; N, 21·8; Cl′, 18·4%). With aqueous sodium iodide it gave the corresponding *iodide hydrochloride* (or *chloride hydriodide*), very pale yellow needles, m. p. 316—317° (from 50% aqueous alcohol) (Found : C, 40·4; H, 4·3; N, 17·3; I, 26·5. $C_{16}H_{19}N_6I,HCl,H_2O$ requires C, 40·4; H, 4·6; N, 17·6; I, 26·6%). Re-treatment of this salt with hot aqueous sodium iodide gave the *iodide hydriodide*, yellowish needles (from water), m. p. 323—324° (Found : C, 34·7; H, 3·9; N, 15·4; I, 44·9. $C_{16}H_{19}N_6I,HI,0{\cdot}5H_2O$ requires C, 34·4; H, 3·8; N, 15·0; I, 45·4%). When the chloride hydrochloride was suspended in hot water at 80°, and sodium carbonate added to faint alkalinity (Brilliant-yellow), it passed transiently into solution and the corresponding *chloride* (V; R = NH_2, R′ = Me, X = Cl) separated; it crystallised from 50% aqueous alcohol as colourless fine needles, m. p. 336—338° (Found : C, 53·9; H, 6·1; N, 22·9; Cl, 10·1. $C_{16}H_{19}N_6Cl,1{\cdot}5H_2O$ requires C, 53·7; H, 6·2; N, 23·5; Cl, 9·9%). A solution of this chloride in water, treated with potassium iodide, gave the iodide as a *monohydrate* but otherwise identical with that obtained in (*a*), m. p. and mixed m. p. 322—323° (Found : C, 43·1; H, 5·1; N, 18·3; I′, 29·0. $C_{16}H_{19}N_6I,H_2O$ requires C, 43·6; H, 4·8; N, 19·1; I′, 28·9%).

6-*Amino*-1 : 2-*dimethylquinol*-4-*one* (IX).—4 : 6-Diamino-1 : 2-methylquinolinium chloride hydrochloride (5 g.) and N-sodium hydroxide (50 c.c.) were boiled together under reflux until evolution of ammonia had ceased (3 hours). The mixture was cooled, and the yellow material which separated was the *quinolone*, yellow prisms, m. p. 321—323° (from water) (Found : C, 70·1; H, 6·4; N, 14·4. $C_{11}H_{13}ON_3$ requires C, 70·05; H, 6·4; N, 14·85%). The same chloride hydrochloride was unchanged by 36% hydrochloric acid at 170—180° (14 hours) or in refluxing aqueous solution at pH 11 (15 minutes).

6-(2-*Amino*-6-*methyl*-4-*pyrimidylamino*)-1 : 2-*dimethylquinol*-4-*one* (X).—(*a*) 6-Amino-1 : 2-dimethylquinol-4-one (0·9 g.), 2-amino-4-chloro-6-methylpyrimidine (0·6 g.), 36% hydrochloric acid (1 c.c.), and water (10 c.c.) were refluxed together for 1 hour, and the solution cooled and made alkaline to Clayton-yellow with sodium hydroxide. The precipitated product was the *quinolone* (X), fine yellow needles (from 50% aqueous alcohol), m. p. 365° (decomp.) (Found : C, 64·5; H, 5·5; N, 23·7. $C_{16}H_{17}ON_5$ requires C, 65·0; H, 5·75; N, 23·7%).

(*b*) 4-Amino-6-(2-amino-6-methyl-4-pyrimidylamino)-1 : 2-dimethylquinolinium iodide (2 g.) and N-sodium hydroxide (50 c.c.) were refluxed together till evolution of ammonia ceased (3 hours). The cooled reaction mixture was filtered, and the solid crystallised from 50% alcohol to give the same material as in (*a*), m. p. and mixed m. p. 365° (decomp.) (Found : N, 24·0%).

4-*Amino*-6-(4-*amino*-6-*methyl*-2-*pyrimidylamino*)-2-*methylquinoline* (III; R = NH_2, R′ = Me).—4 : 6-Diamino-2-methylquinoline (4·2 g.), 4-amino-2-chloro-6-methylpyrimidine (3·4 g.) (Gabriel and Colman, *loc. cit.*), water (50 c.c.), and 36% hydrochloric acid (6 c.c.) were boiled together under reflux for 4 hours. After cooling, the colourless crystalline *dihydrochloride* which

had separated was washed with acetone and gave needles (5 g.), m. p. >300° (previous loss of water), from 50% aqueous alcohol (Found, in material dried at 100°: C, 47·75; H, 5·7; N, 21·9; Cl, 18·5. $C_{15}H_{16}N_6,2HCl,1·5H_2O$ requires C, 47·3; H, 5·5; N, 22·1; Cl, 18·7%). The *base*, obtained by addition of sodium hydroxide to a solution of the hydrochloride in water, crystallised from alcohol as very pale yellow prisms, m. p. 272—273° (Found: C, 56·8; H, 6·3; N, 26·4. $C_{15}H_{16}N_6,2H_2O$ requires C, 57·0; H, 6·3; N, 26·6%).

4-Amino-6-(4-amino-6-methyl-2-pyrimidylamino)-1 : 2-dimethylquinolinium Salts (VI; R = NH_2, R′ = Me).—(*a*) The above base (3 g.), methyl iodide (7 c.c.), and alcohol (50 c.c.) were refluxed together for 6 hours. After cooling, the product was collected, washed with acetone, dried, and crystallised from 50% aqueous alcohol containing a few drops of ammonia. The *iodide* formed pale yellow needles (2·3 g.), m. p. 340° (decomp.) with previous softening (Found: C, 45·5; H, 4·5; N, 19·8; I, 30·2. $C_{16}H_{19}N_6I$ requires C, 45·6; H, 4·5; N, 19·9; I, 30·2%).

(*b*) 4-Amino-2-chloro-6-methylpyrimidine (3·6 g.), 4 : 6-diamino-1 : 2-dimethylquinolinium chloride (5·6 g.), water (50 c.c.), and 36% hydrochloric acid (6 c.c.) were heated together at 100° for 1 hour. The product which separated was collected, after cooling, washed with acetone, and crystallised from 75% aqueous alcohol to give the *hydrochloride* of the chloride (VI; R = NH_2, R′ = Me, X = Cl) (7·5 g.) as fine colourless needles, m. p. 366° (decomp.) (Found: C, 48·0; H, 6·0; N, 21·0; Cl, 17·0. $C_{16}H_{19}N_6Cl,HCl,2H_2O$ requires C, 47·7; H, 6·0; N, 20·8; Cl, 17·6%). When treated in hot water with sodium carbonate to alkalinity to Brilliant-yellow, this salt gave the *chloride* (VI; R = NH_2, R′ = Me, X = Cl), which separated from 50% aqueous alcohol as yellow prisms, m. p. >380° (Found: C, 58·0; H, 5·6; N, 25·0; Cl, 10·5. $C_{16}H_{19}N_6Cl$ requires C, 58·2; H, 5·75; N, 25·4; Cl, 10·75%). The corresponding iodide, after crystallisation from 50% aqueous alcohol, was identical with that made by method (*a*), m. p. and mixed m. p. 340° (decomp.) (Found: C, 45·3; H, 4·5; N, 19·9; I, 30·2%).

4-Amino-6-(4-amino-2-methyl-6-pyrimidylamino)-2-methylquinoline (XI; R = NH_2, R′ = R″ = Me).—4 : 6-Diamino-2-methylquinoline (3·5 g.), 6-amino-4-chloro-2-methylpyrimidine (2·9 g.) (Baddiley, Lythgoe, McNeil, and Todd, *J.*, 1943, 383), water (50 c.c.), and 10N-hydrochloric acid (2·2 c.c.) were boiled together under reflux for 4 hours. After cooling, the product was collected and crystallised from 50% aqueous alcohol to give the *dihydrochloride* as pale yellow needles, m. p. >380° (Found: C, 42·8; H, 6·2; N, 19·9; Cl′, 16·9, 17·0. $C_{15}H_{16}N_6,2HCl,3·5H_2O$ requires C, 43·1; H, 6·0; N, 20·2; Cl′, 17·1%). The corresponding *base*, obtained by rendering a solution of the hydrochloride alkaline to Clayton-yellow, crystallised from 50% aqueous alcohol as fine colourless needles, m. p. 292—294° (Found: C, 62·9; H, 5·9; N, 29·0. $C_{15}H_{16}N_6,0·5H_2O$ requires C, 62·3; H, 5·9; N, 29·0%).

4-Amino-6-(4-amino-2-methyl-6-pyrimidylamino)-1 : 2-dimethylquinolinium Salts (XII; R = NH_2, R′ = R″ = Me).—(*a*) The preceding compound (6 g.), methyl iodide (10 c.c.), and alcohol (100 c.c.) were refluxed on the steam-bath overnight. Rapid dissolution occurred, followed shortly by deposition of the *iodide*. After cooling, this was collected; it crystallised from 50% aqueous alcohol as yellow needles, m. p. 344° (decomp.) (Found: C, 43·8; H, 5·0; N, 18·7; I, 28·6. $C_{16}H_{19}N_6I,H_2O$ requires C, 43·7; H, 4·8; N, 19·1; I, 28·9%). In another experiment it was obtained as the *dihydrate* (Found: C, 42·5; H, 4·8; N, 18·6; I′, 27·6. $C_{16}H_{19}N_6I,2H_2O$ requires C, 41·9; H, 5·0; N, 18·3; I′, 27·7%).

(*b*) 4 : 6-Diamino-1 : 2-dimethylquinolinium chloride hydrochloride (5·6 g.), 6-amino-4-chloro-2-methylpyrimidine (3·6 g.), and water (50 c.c.) were boiled under reflux for 2 hours. The product which separated on cooling was collected and dissolved in boiling water, and the solution made alkaline to Brilliant-yellow with sodium carbonate and salted out with sodium chloride. The precipitated *chloride* (XII; R = NH_2, R′ = R″ = Me, X = Cl) crystallised from 50% aqueous alcohol as colourless fine needles which became yellow at 100°, and had m. p. 358° (decomp.) (Found, in air-dried material: C, 54·8; H, 6·0; N, 23·8; Cl, 10·6. $C_{16}H_{19}N_6Cl,H_2O$ requires C, 55·1; H, 6·0; N, 24·1; Cl, 10·2%). It was converted into the corresponding *iodide* by the usual method; m. p. 344° (decomp.) undepressed on admixture with material made by method (*a*) (Found: C, 43·0, 43·1; H, 4·6; N, 18·7; I, 28·1. $C_{16}H_{19}N_6I,1·5H_2O$ requires C, 43·0; H, 4·9; N, 18·7; I, 28·3%).

4-Amino-6-(2 : 6-diamino-4-pyrimidylamino)-2-methylquinoline (XI; R = R″ = NH_2, R′ = Me).—4 : 6-Diamino-2-methylquinoline hydrochloride (10·2 g.), 2 : 6-diamino-4-chloropyrimidine (6·7 g.) (Hull, Lovell, Openshaw, and Todd, *J.*, 1947, 41), and acetic acid (9 c.c.) were heated together at 150—160° for 16 hours. The mixture rapidly became fluid and thereafter gradually solidified. The cooled mixture was dissolved in hot water, and the solution treated with carbon, filtered, and made alkaline with sodium hydroxide. The product, initially precipitated as an oil, rapidly solidified and was then collected, washed with water, and boiled with a little 50%

alcohol. The insoluble material (9·4 g.), m. p. 335—336° (decomp.), crystallised from propanol to give the *product* as a buff-coloured powder of unchanged m. p. (Found : C, 59·5; H, 5·4; N, 34·2. $C_{14}H_{15}N_7$ requires C, 59·8; H, 5·35; N, 34·9%).

4-Amino-6-(2 : 6-diamino-4-pyrimidylamino)-1 : 2-dimethylquinolinium Iodide (XII; R = R'' = NH_2, R' = Me, X = I).—4 : 6-Diamino-1 : 2-dimethylquinolinium chloride hydrochloide (4 g.), 2 : 6-diamino-4-chloropyrimidine (2·2 g.), and acetic acid (3·1 c.c.) were stirred and heated together at 150—160° for 2 hours, the original fluid melt then having solidified. The cooled reaction mixture was dissolved in hot water, sodium carbonate added to make the solution alkaline to litmus, and excess of sodium iodide added. The precipitated *iodide* was filtered off when cold, and crystallised from 50% aqueous alcohol (XII; R = R'' = NH_2, R' = Me, X = I) as a colourless powder (2·65 g.), m. p. 314° (decomp.) (Found : C, 41·4; H, 4·4; N, 22·7; I, 28·7. $C_{15}H_{18}N_7I,0·5H_2O$ requires C, 41·7; H, 4·4; N, 22·7; I, 29·4%).

6-Amino-1 : 2-dimethylquinolinium Chloride.—A suspension of 6-acetamido-2-methylquinoline (30·4 g.) (Hamer, *J.*, 1921, **119**, 1436) in nitrobenzene (150 c.c.) was heated on the steam-bath till dissolved; methyl sulphate (16 c.c.) was added, and heating continued for ½ hour. Rapid separation of colourless crystalline material took place. The solid was filtered from the cooled mixture, washed with acetone, and dried. A solution of this product in 20% hydrochloric acid (160 c.c.) was boiled for 15 minutes and cooled. The precipitate was washed with acetone, and crystallised from 20% hydrochloric acid to give *6-amino-1 : 2-dimethylquinolinium chloride hydrochloride* as pale buff needles, m. p. 267° (decomp.) (Found : C, 49·8; H, 6·25; N, 10·2; Cl, 26·2. $C_{11}H_{13}N_2Cl,HCl,H_2O$ requires C, 50·2; H, 6·1; N, 10·6; Cl, 27·0%). A solution of this hydrochloride in water was made alkaline with sodium carbonate, and sodium chloride added. The precipitated *6-amino-1 : 2-dimethylquinolinium chloride* crystallised from 95% ethanol as brownish-yellow needles, m. p. 282—283° (Found : C, 58·4; H, 6·65; N, 12·55; Cl, 15·8. $C_{11}H_{13}N_2Cl$ requires C, 58·3; H, 6·6; N, 12·4; Cl, 15·7%).

6-(2-Amino-6-methyl-4-pyrimidylamino)-1 : 2-dimethylquinolinium Chloride (V; R = H, R' = Me, X = Cl).—6-Amino-1 : 2-dimethylquinolinium chloride (4·2 g.), 2-amino-4-chloro-6-methylpyrimidine (2·8 g.), water (25 c.c.), and 36% hydrochloric acid (3 c.c.) were refluxed together for 1 hour. The solution was made alkaline with sodium hydrogen carbonate and cooled. The *chloride* which separated crystallised from 50% aqueous alcohol in yellow needles, m. p. 304—305° (Found : C, 53·3; H, 6·6; N, 19·3; Cl, 10·2. $C_{16}H_{18}N_5Cl$ requires C, 53·3; H, 6·4; N, 19·4; Cl, 9·8%).

6-(4-Amino-6-methyl-2-pyrimidylamino)-1 : 2-dimethylquinolinium Iodide (VI; R = H, R' = Me, X = I).—6-Amino-1 : 2-dimethylquinolinium chloride hydrochloride (5 g.), 4-amino-2-chloro-6-methylpyrimidine (2·8 g.), water (25 c.c.), and 36% hydrochloric acid (1 c.c.) were boiled together under reflux for 1 hour. The reaction mixture was made alkaline to Brilliant-yellow with sodium carbonate, and potassium iodide added. The precipitated *iodide* crystallised from 50% aqueous alcohol in yellow needles, m. p. 246—248° (Found : C, 45·5, 45·6; H, 4·8, 4·7; N, 16·7. $C_{16}H_{18}N_5I,H_2O$ requires C, 45·2; H, 4·7; N, 16·5%).

6-(2-Amino-6-methyl-4-pyrimidylamino)quinoline (II; R = R' = H).—2-Amino-4-chloro-6-methylpyrimidine (7·2 g.) and 6-aminoquinoline hydrochloride (9 g.) in water (50 c.c.) and 36% hydrochloric acid (1 c.c.) were similarly condensed. The resulting clear solution was treated with carbon, filtered, and made alkaline with ammonia. The precipitated oily *product* quickly solidified and crystallised from alcohol as yellowish needles, m. p. 233—234° (Found : C, 64·7; H, 5·6; N, 26·8. $C_{14}H_{13}N_5,0·5H_2O$ requires C, 64·6; H, 5·4; N, 26·9%).

6-Acetamido-1-methylquinolinium Iodide.—To 6-acetamidoquinoline (18·6 g.) in nitrobenzene (100 c.c.) at 100° methyl sulphate (15 c.c.) was added during 5 minutes with stirring, which was continued for 3 hours. The mixture was cooled, and the almost colourless quaternary methosulphate was collected, washed with acetone, and dried. It was dissolved in a small volume of cold water, the solution treated with carbon and filtered, and excess of potassium iodide added. The precipitated *iodide* crystallised from water as yellow tablets, decomp. >280° (Found : C, 43·9; H, 3·9; N, 8·8; I, 38·9. $C_{12}H_{13}ON_2I$ requires C, 43·9; H, 3·95; N, 8·55; I, 38·8%).

6-Amino-1-methylquinolinium Salts.—The crude methosulphate prepared as described in the preceding experiment (12 g.), water (10 c.c.), and hydrochloric acid (20 c.c.) were boiled together for 10 minutes. The solution was cooled, and acetone (50 c.c.) was added to precipitate *6-amino-1-methylquinolinium chloride hydrochloride* (6·2 g.), m. p. 246—247° (decomp.). This crystallised from 36% hydrochloric acid–ethanol (1 : 1) as colourless prisms, m. p. 246—247° (decomp.) (Found : C, 52·1; H, 5·1; N, 12·1. $C_{10}H_{11}N_2Cl,HCl$ requires C, 52·0; H, 5·2; N, 12·1%). The hydrochloride (2 g.) was dissolved in water (10 c.c.), and the solution made alkaline with sodium carbonate and divided into two portions. Addition of sodium chloride to

one portion, and recrystallisation of the product from ethanol, gave *6-amino-1-methylquinolinium chloride* as long yellow prisms, m. p. 244° (Found: C, 56·05; H, 6·15; N, 13·15; Cl, 16·0. $C_{10}H_{11}N_2Cl,H_2O$ requires C, 56·5; H, 6·1; N, 13·2; Cl, 16·7%). The other portion with sodium iodide gave the *iodide* as orange needles, m. p. 194—195°, from ethanol (Found: C, 39·9; H, 4·15; N, 9·55. $C_{10}H_{11}N_2I,H_2O$ requires C, 39·5; H, 4·3; N, 9·2%).

6-(2-Amino-6-methyl-4-pyrimidylamino)-1-methylquinolinium Salts (V; R = R′ = H).—(*a*) 6-Amino-1-methylquinolinium chloride (4 g.) and 2-amino-4-chloro-6-methylpyrimidine (2·8 g.) were heated in boiling water (25 c.c.) containing 36% hydrochloride acid (3 c.c.) for 1 hour, and the mixture made alkaline with sodium hydrogen carbonate and cooled. The product which separated was washed with acetone and crystallised from 50% aqueous alcohol to give the *chloride* (V; R = R′ = H, X = Cl) as golden-yellow needles (6·6 g.), m. p. 277—278° (Found: C, 53·5; H, 6·3; N, 20·4. $C_{15}H_{16}N_5Cl,2H_2O$ requires C, 53·35; H, 5·9; N, 20·7%). The corresponding *iodide* (V; R = R′ = H, X = I) crystallised from 50% aqueous alcohol as orange needles, m. p. 258—259° (Found: C, 42·4; H, 4·9; N, 16·7; I, 29·5. $C_{15}H_{16}N_5I,2H_2O$ requires C, 42·0; H, 4·7; N, 16·3; I, 29·6%).

(*b*) 6-(2-Amino-6-methyl-4-pyrimidylamino)quinoline (4 g.) and methyl sulphate (2 g.) were heated together in nitrobenzene (50 c.c.) at 100—110° for 10 minutes; the deep yellow solid formed was then completely soluble in water. After cooling, it was filtered off, washed with acetone, and dried. This methyl methosulphate was dissolved in water, and potassium iodide added. The precipitated methiodide, crystallised from water, had m. p. 256—258° undepressed on admixture with material made by method (*a*).

(*c*) 6-(2-Amino-6-methyl-4-pyrimidylamino)quinoline (2 g.), methyl iodide (1·5 c.c.), and alcohol (20 c.c.) were heated together in a sealed tube for 6 hours at 100°. After cooling, the product which had separated was washed with alcohol and crystallised from water to give *6-(2-amino-6-methyl-4-pyrimidylamino)-1-methylquinolinium iodide hydriodide* as orange needles, m. p. 314—315° (decomp.) (Found: C, 32·9; H, 3·8; N, 12·9; I, 45·5. $C_{15}H_{16}N_5I,HI,1·5H_2O$ requires C, 32·9; H, 3·7; N, 12·8; I, 45·4%).

(*d*) 6-(2-Amino-6-methyl-4-pyrimidylamino)quinoline (2·5 g.), methyl iodide (14 c.c.), and alcohol (50 c.c.) were refluxed together on the steam-bath for 18 hours. After about 1 hour deep yellow crystalline material separated, but on further refluxing this was replaced by a voluminous microcrystalline product. After cooling, this was collected and crystallised from water to give the hydriodide of (V; R = R′ = H, X = I), m. p. 315° (decomp.) undepressed on admixture with the product from (*c*) (Found: I, 46·0%). When this salt was dissolved in water and made alkaline with sodium hydrogen carbonate, and the product crystallised from 50% aqueous alcohol, it gave 6-(2-amino-6-methyl-4-pyrimidylamino)-1-methylquinolinium iodide, m. p. 257° undepressed on admixture with material made by method (*a*).

6-(4-Amino-6-methyl-2-pyrimidylamino)quinoline (III; R = R′ = H).—(*a*) 6-Aminoquinoline (1·55 g.), 4-amino-2-chloro-6-methylpyrimidine (1·45 g.), and aqueous N-hydrochloric acid (11 c.c.) were boiled under reflux for 3 hours. A thick precipitate of yellow crystalline plates was deposited on cooling. These were washed with water, dried, and crystallised from water; the *dihydrochloride* was obtained as yellow plates (2·05 g.), m. p. >360° (Found: C, 48·9; H, 5·25; N, 20·2; Cl, 20·7. $C_{14}H_{13}N_5,2HCl,H_2O$ requires C, 49·1; H, 5·0; N, 20·5; Cl, 20·7%). Its solution was made alkaline with sodium hydroxide; an oil was precipitated, and on standing it solidified and was crystallised from 50% aqueous alcohol, giving the hydrated *base* as pale green prisms, m. p. 100—103° (Found: C, 62·4; H, 5·6; N, 25·9. $C_{14}H_{13}N_5,H_2O$ requires C, 62·5; H, 5·6; N, 26·0%).

(*b*) 6-(4-Chloro-6-methyl-2-pyrimidylamino)quinoline (5 g.) (Curd *et al.*, *J.*, 1947, 1613) and concentrated ammonia (25 c.c.) were heated in a sealed tube at 175° for 12 hours. The product, which separated, on cooling, initially as an oil, gradually solidified and was then purified as under (*a*) to give the same material, m. p. and mixed m. p. 100—101°.

6-(4-Amino-6-methyl-2-pyrimidylamino)-1-methylquinolinium Iodide (VI; R = R′ = H, X = I).—(*a*) 6-Amino-1-methylquinolinium chloride (1·9 g.), 4-amino-2-chloro-6-methylpyrimidine (1·4 g.), water (20 c.c.), and 36% hydrochloric acid (1·5 c.c.) were refluxed for 1 hour. While still warm, the mixture was made alkaline with sodium hydrogen carbonate, and potassium iodide added to precipitate the *iodide* which crystallised from water as yellow needles, m. p. 285—286° (Found: C, 45·65; H, 4·45; N, 17·85; I, 32·5. $C_{15}H_{16}N_5I$ requires C, 45·8; H, 4·1; N, 17·8; I, 32·3%).

(*b*) 6-(4-Amino-6-methyl-2-pyrimidylamino)quinoline (3 g.), alcohol (50 c.c.), and methyl iodide (7 c.c.) were refluxed on the steam-bath for 16 hours. The yellow material which had separated crystallised from water to give the *hydriodide* of the iodide (VI; R = R′ = H, X = I)

as yellow needles, m. p. *ca.* 285° (decomp.) (Found: C, 35·2; H, 3·7; N, 13·5; I, 48·3. $C_{15}H_{16}N_5I,HI$ requires C, 34·6; H, 3·3; N, 13·4; I, 48·8%). A solution of this iodide hydriodide in water was made alkaline with sodium hydrogen carbonate and treated with potassium iodide to give the iodide, which, crystallised from water, had m. p. 285—286° undepressed on admixture with material made by method (*a*).

6-(6-*Amino-2-methyl-4-pyrimidylamino*)*quinoline* (XI; R = R′ = H, R″ = Me).—6-Aminoquinoline hydrochloride (10 g.) and 4-amino-6-chloro-2-methylpyrimidine (7·2 g.) were intimately mixed by grinding, acetic acid (10 c.c.) was added, and the mixture heated at 150—160° for 3 hours with stirring. The whole became fluid below 100° but gradually solidified later. After cooling, the mass was dissolved in water, and the solution treated with carbon and filtered. Addition of sodium hydroxide to the filtrate precipitated the *base* as an oil. This rapidly solidified and was then washed with water, dried, and crystallised from methanol to give yellow laminæ (12·3 g.), m. p. 229—230° (Found: C, 66·6; H, 5·0; N, 27·8. $C_{14}H_{13}N_5$ requires C, 67·0; H, 5·2; N, 27·8%).

6-(6-*Amino-2-methyl-4-pyrimidylamino*)-1-*methylquinolinium Iodide* (XII; R = R′ = H, R″ = Me, X = I).—The preceding base (3 g.), methyl iodide (7 c.c.), and alcohol (50 c.c.) were refluxed on the steam-bath for 18 hours. The product, which separated rapidly, was collected hot, washed, and dissolved in water (200 c.c.). Addition of sodium hydrogen carbonate precipitated the *iodide*, which crystallised from water in yellow needles (2 g.), m. p. 291—292° (decomp.) (Found: C, 45·6; H, 4·4; N, 17·7; I′, 31·7. $C_{15}H_{16}N_5I$ requires C, 45·7; H, 4·1; N, 17·8; I′, 32·3%).

6-(2 : 6-*Diamino-4-pyrimidylamino*)*quinoline* (XI; R = R′ = H, R″ = NH_2).—6-Aminoquinoline hydrochloride (9 g.) and 2 : 6-diamino-4-chloropyrimidine (7 g.) were condensed together as for the 2-methyl compound above (acetic acid, 5 c.c.; 18 hours' heating at 130—140°), and the product worked up as before, but the base was precipitated by ammonia; the oil rapidly solidified, and after collection, washing, and drying, was crystallised from alcohol (yield, 5·7 g.; m. p. 240—245°). A small quantity was sublimed at 180°/0·1 mm., and the sublimate crystallised from alcohol, giving 6-(2 : 6-*diamino-4-pyrimidylamino*)*quinoline* as colourless plates, m. p. 248—249° (Found: C, 61·5; H, 4·75; N, 33·3. $C_{13}H_{13}N_6$ requires C, 61·9; H, 4·75; N, 33·3%).

6-(2 : 6-*Diamino-4-pyrimidylamino*)-1-*methylquinolinium Iodide* (XII; R = R′ = H, R″ = NH_2, X = I).—(*a*) 6-Amino-1-methylquinolinium chloride hydrochloride (1 g.) and 2 : 6-diamino-4-chloropyrimidine (0·7 g.) were condensed together as above (acetic acid, 1·0 c.c.; 2 hours' heating at 150—160°). The melt first obtained set to a solid mass, which was dissolved in water. The solution was treated with carbon, filtered, and made alkaline with sodium carbonate, and sodium iodide was added. The precipitate was washed with water and crystallised from water to give the *iodide* (XII; R = R′ = H, R″ = NH_2, X = I) as yellow plates (1·1 g.), m. p. 281° (Found: C, 39·8; H, 4·7; N, 20·1; I, 30·95. $C_{14}H_{15}N_6I,1{\cdot}5H_2O$ requires C, 39·9; H, 4·3; N, 20·0; I, 30·1%).

(*b*) 6-(2 : 6-Diamino-4-pyrimidylamino)quinoline (3 g.), methyl iodide (7 c.c.), and ethanol (50 c.c.) were refluxed together on the steam-bath for 6 hours. The yellow granular material which had separated was filtered off and dissolved in water, and the solution made faintly alkaline with sodium hydrogen carbonate. The precipitate was collected and recrystallised from water to give a product of m. p. 281°, identical with that under (*a*).

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